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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,464	10/18/2001	William D. Huse	AME-06381	7635

23535 7590 03/13/2003

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EXAMINER
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HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 03/13/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/982,464

**Applicant(s)**

HUSE ET AL

**Examiner**

Larry R. Helms

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 January 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_                      6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

***Election/Restrictions***

1. Applicant's election with traverse of Group I, claims 1-6 and 13-18 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that both groups I and II are in the same class and subclass and that the examiner has not provided any evidence to support separate status in the art. This is found persuasive and all claims will be examined.
2. Claims 1-24 are pending and under examination.

***Oath/Declaration***

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the oath/declaration does not list the provisional application 60/159,689 for which priority is being requested.

***Specification***

4. The amendment filed 4/16/02 requested that a paragraph on page 65, line 2 to page 66 be deleted and replaced by a new paragraph (see page 2 of amendment). This part of the amendment was not entered because original page 65 is a claim page and there was no paragraph to replace. Applicant is requested to clarify this issue.

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5. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: It is unclear where the limitation of representation is or representation in electronic form as in claims 1, 2, 7, 8, 13, 14, 19, 20.

***Notice***

6. It is requested that the letters recited in the claims for parts a-d (claims 1, 7, 13, 19) and parts e (claims 3, 9, 15, 21) be uniform as either all capital letters or all lower case letters.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 3-7, 9-13, 15-19, 21-24 are indefinite for reciting "providing a representation" in claims 1, 7, 13, 19 because the exact meaning of the phrase is not clear. Does the phrase mean a picture, a sequence on paper, a thought pattern?

b. Claims 1, 7, 13, 19 recites the limitation "said first reference sequence" in the claims (see for example claim 1, line 4). There is insufficient antecedent basis for this limitation in the claims.

c. Claims 1, 7, 13, 19 recites the limitation "said second reference sequence" in the claims (see for example claim 1, line 7). There is insufficient antecedent basis for this limitation in the claims.

d. Claims 1 and 7 and those claims depending on claims 1 and 7 are indefinite for reciting "said acceptor heavy chain" in line 11 and "said second reference sequence" in line 12 because the exact meaning of the phrases are not clear. It is unclear how the acceptor heavy chain variable region is different from the second reference sequence because as recited in the claims in line 7-8 the second reference sequence comprises the acceptor heavy chain.

e. Claims 13, 19 recites the limitation "said modified first complementarity-determining region" in the claims (see line 11-12). There is insufficient antecedent basis for this limitation in the claims.

### ***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by

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another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 3-7, 9-13, 15-19, 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Aruffo et al (U.S. Patent 6,312,693, filed 2/1999).

The claims recite a method of constructing a population of heavy or light chain variable region encoding nucleic acids comprising providing a donor sequence and an acceptor sequence and chemically synthesizing a population of oligos encoding for at least one modified CDR wherein at least one amino acid is different from the reference sequence and a second population of oligos encoding unmodified framework regions and mixing to create overlapping oligos and constructing the nucleic acids. Further co expressing the population with a light or heavy chain and wherein the acceptor is human and further the method comprises extending the oligos with polymerase.

Aruffo et al teach a method of constructing a library of heavy or light chain regions wherein one CDR is mutated and the frameworks are non modified relative to the reference human sequence and expression of the heavy and light chains and the oligos are overlapping and extended by PCR (see column 27-28).

***Claim Rejections - 35 USC § 103***

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11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Nature 321:522, 1986) and further in view of Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and Soderlind et al (Gene 160:269-72, 1995) and Hagiwara et al (U.S. Patent 5,589,573, issued 12/96).

Claims 1, 3-7, 9-13, 15-19, 21-24 have been described supra. Claims 2, 8, 14, 20 recite wherein the representation is in electronic form.

Jones et al teach CDR grafting of non-human CDRs into human frameworks by comparing the rodent and human sequences and producing the antibodies by synthesizing oligonucleotides and the affinity of the humanized antibody is lower than that of the parent. Jones et al does not teach a library with mutations in the CDRs and no mutations in the frameworks or construction by overlapping oligos or representation in electronic form. These deficiencies are made up for in the teachings of Yelton et al, Soderlind et al and Hagiwara et al.

Yelton et al teach affinity maturation of an antibody by mutagenesis in the CDRs and construction of random libraries in the heavy chain and they intend to examine the light chain (see entire document and page 2002, left column).

Soderlind et al teach libraries of variable domains wherein the CDRs are mutagenized and the frameworks were unchanged and the libraries were made by overlapping oligos (see entire document).

Hagiwara et al teach amino acid sequences from a database of Kabat et al and the sequences are retrievable by computer (see column 12, lines 25-40).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have constructed a library of heavy or light chain amino acid sequence wherein the CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing a electronic form of the



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reference sequences in view of the teachings of Jones et al, Yelton et al, Soderlind et al, and Hagiwara et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have constructed a library of heavy or light chain amino acid sequence wherein the CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing a electronic form of the reference sequences in view of the teachings of Jones et al, Yelton et al, Soderlind et al, and Hagiwara et al because Jones et al teach CDR grafting onto a human framework and the antibody has a lower affinity than the murine antibody and it would be obvious to use the mutagenesis strategy of Yelton et al to produce a library of CDR mutants and keep the framework residues constant because Yelton et al teach antibodies which resulted in improved affinity only by altering the CDRs. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have constructed a library of heavy or light chain amino acid sequence wherein the CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing a electronic form of the reference sequences in view of the teachings of Jones et al, Yelton et al, Soderlind et al, and Hagiwara et al because Soderlind et al teach a variable region library for an antibody produced by synthesizing overlapping oligos which resulted in construction of the library in one single PCR (see abstract) and the method resulted in a divers library in the CDRs (see page 271).

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Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have constructed a library of heavy or light chain amino acid sequence wherein the CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing an electronic form of the reference sequences in view of the teachings of Jones et al, Yelton et al, Soderlind et al, and Hagiwara et al because Hagiwara et al teach amino acid sequences from a database of Kabat et al and the sequences are retrievable by computer (see column 12, lines 25-40). In addition, because the database is accessible by computer it would be obvious to download the sequences onto an electronic form for storage and manipulation. Thus, it would have been obvious to produce a library wherein the CDRs are altered and the frameworks are not as taught by Yelton et al and Soderlind et al and the frameworks are from a human antibody as taught by Jones et al and produce the library for screening for increased affinity and provide an electronic form of the sequences as taught by Hagiwara et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

13. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aruffo et al (U.S. Patent 6,312,693, filed 2/99) as applied to claims 1, 3-7, 9-13, 15-19, 21-24 above, and further in view of Hagiwara et al (U.S. Patent 5,589,573, issued 12/96).

The claims have been described supra.

Aruffo et al has been described supra. Aruffo et al does not teach the reference sequence in electronic form. This deficiency is made up for in the teachings of Hagiwara et al.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have the first and second reference sequences to be in electronic form.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have the first and second reference sequences to be in electronic form because Hagiwara et al teach amino acid sequences from a data base of Kabat et al and the sequences are retrievable by computer (see column 12, lines 25-40). In addition, because the database is accessible by computer it would be obvious to download the sequences onto an electronic form for storage and manipulation.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Conclusion***

14. No claim is allowed.

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15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

A handwritten signature in black ink, appearing to be 'L. Helms', written in a cursive style.